Differentiating Toxicities of Conazole Fungicides Through Metabonomic Analyses of Multiple Tissues

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The conazole fungicides represent a large group of compounds widely used agriculturally for the protection of crop plants (Hutson, 1998) and pharmaceutically in the treatment of topical and systemic infections (Sheehan, 1999). In 1999, the latest period for which agricultural usage estimates are available, 79 and 556 million pounds of fungicide active ingredient were used in the U.S. and world markets, respectively (Donaldson, 2002), creating concern over the impact these compounds may have through environmental exposure to humans and other organisms. In an attempt to better understand the toxicities of these compounds, an NMR (Nuclear Magnetic Resonance)-based metabonomics approach was used to determine differences in the toxicities of two conazole fungicides (myclobutanil and triadimefon) by analyses of metabolite changes occurring in blood serum, liver tissue, and testicular tissue of control and exposed rats. Metabonomics is the quantitative measurement of a broad spectrum of metabolic responses of living systems in response to disease onset or genetic modification. By monitoring changes in cellular metabolites in response to the introduction of a toxicant, the biochemical pathways affected can be determined and the specific toxic response characterized on a molecular level. Furthermore, metabonomic data can be used in conjunction with genomic and proteomic data to more fully characterize environmental effects. Through the combined efforts of the U.S. Environmental Protection Agency (U.S. EPA), the Procter and Gamble Company, and the Imperial College (London, England), distinct metabolite profiles produced by exposure to conazole fungicides were identified. These metabonomic profiles identify potential biological pathways responding to the exposures. One distinct change observed was induction of betaine levels in rats exposed to myclobutanil versus those exposed to triadimefon or control rats. This betaine effect indicates altered homocysteine metabolism. Homocysteine is an intermediate metabolite of the amino acid methionine, and altered homocysteine levels have been linked to a variety of health problems. These preliminary results support the case for metabonomics as part of the Computational Toxicology program in the ORD and suggest the potential of metabonomics for assessing the toxicity of compounds regulated by the U.S. EPA.